Serious stomatitis and esophagitis: a peculiar mucous reaction induced by pegylated liposomal doxorubicin*

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Abstract: Pegylated liposomal doxorubicin is an important antineoplastic agent with activity in a variety of solid tumors. It has a totally different profile of pharmacokinetics and toxicity compared with doxorubicin. It rarely causes side-effects like cardiotoxicity or hair loss, but frequently results in many kinds of mucocutaneous reactions, including palmar-plantar erythrodysesthesia, diffuse follicular rash, intertrigo-like eruption, new formation of melanotic macules, stomatitis and radiation recall dermatitis. We present a rare case of multiple myeloma who immediately developed serious stomatitis and esophatitis associated with minor palmar-plantar erythrodysesthesia after a single course of pegylated liposomal doxorubicin.
Keywords: Doxorubicin; Esophagitis; Stomatitis

INTRODUCTION

Pegylated liposomal doxorubicin is an encapsulation form of doxorubicin. It has a totally different profile of pharmacokinetics and toxicity. Adverse reactions are predominantly six patterns of mucocutaneous eruptions, including palmar-plantar erythrodysesthesia (PPE), diffuse follicular rash, intertrigo-like eruption, new formation of melanotic macules, stomatitis and radiation recall dermatitis.[1] We present a rare case of multiple myeloma (MM) who immediately developed serious stomatitis and esophatitis associated with minor PPE after a single course of pegylated liposomal doxorubicin.

CASE REPORT

A 69-year-old female presented with lower back pain for five months. Laboratory examination showed elevated serum IgG (66.1 g/L). Serum immunofixation revealed a characteristic pattern of monoclonal IgG gammopathy, particularly of λ paraprotein. Magnetic resonance imaging (MRI) suggested minor compression fractures of the T_{12} and L_3 vertebral bodies and a geographic osteolytic lesion involving almost the whole thoracic, lumbar and sacral vertebrae. Subsequently, positron emission/tomography computed tomography (PET/CT) scan showed multiple areas of abnormal uptake in the T_{12} and L_3 vertebral bodies, left sternoclavicular joint and pubic symphysis. A bone marrow aspirate revealed active myeloid proliferation and 33% of plasmacytes. The patient was diagnosed with MM and VADM chemotherapy was delivered as follows: vincristine 0.5 mg d1-4, pegylated liposomal doxorubicin 15 mg d1-4, dexamethasone 10 mg d1-4 and melphalan 6mg twice a day d1-4.

On the third day of the chemotherapy course, the patient complained of subxiphoid pain while swallowing. Two days after the last infusion of chemotherapy drugs, the patient began to present neutropenic fever, developed multiple painful oral ulcers and showed no response to many kinds of broad-spectrum antibiotics (Figure 1). One week later, minor PPE with asymptomatic desquamation was observed. Gastroscopic observation revealed serious, anular, geographic ulcers in the mid/distal esophagus and chronic stomach inflammation (Figures 1 and 2). Histopathologic examination of the esophageal tissue

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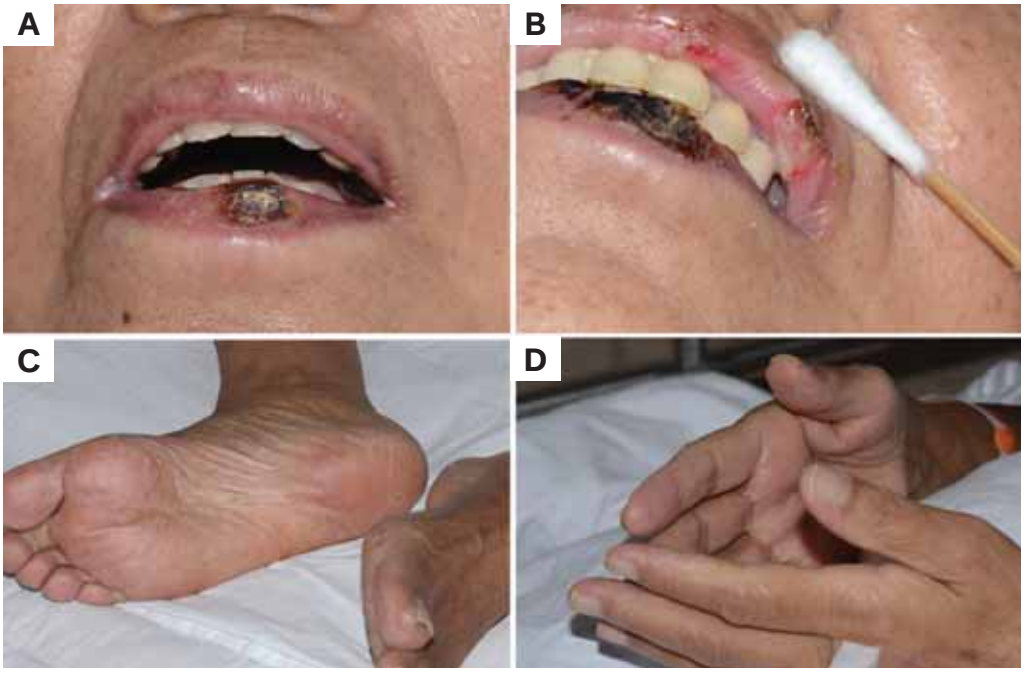

Figure 1: Multiple painful oral ulcers **(A and B)**. Minor PPE with asymptomatic desquamation **(C and D)**

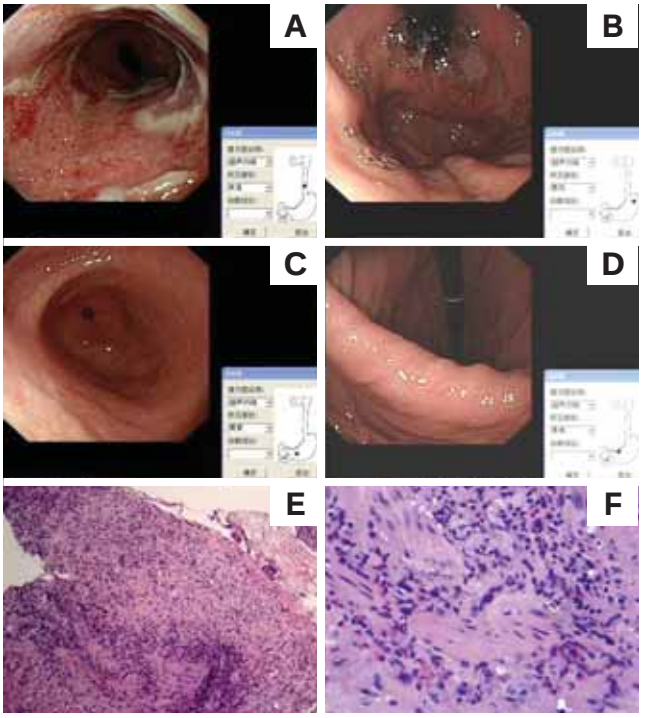

Figure 2: Gastroscopic observation. Annular, geographic ulcers in the mid **(A)** and distal **(B)** esophagus. Chronic stomach inflammation **(C and D)**. Histopathologic examination of the esophageal tissue. **(E)** Superficial tissue necrosis, formation of granulation tissue (hematoxylin-eosin stain, original magnification×100). **(F)** Lymphocytes, histiocytes and eosinophils infiltrated into the connective tissue (hematoxylin-eosin stain, original magnification×400)

revealed superficial tissue necrosis, formation of granulation tissue and a lot of lymphocytes, histiocytes and eosinophils infiltrated into the connective tissue (Figure 2). Two more weeks later, all the aforementioned symptoms resolved spontaneously without any special treatments. One month later, the patient received the second course of chemotherapy and was switched to CTD in consideration of side-effects: cyclophosphamide 1.2 g d1, thalidomide 200 mg d1-28 and dexamethasone 20 mg d1-4. No similar symptoms came again.

DISCUSSION

The pegylated liposomal form of doxorubicin is an important antineoplastic agent with activity in a variety of solid tumors, such as metastatic breast cancer, aggressive Non-Hodgkin lymphoma, non-small cell lung cancer, multiple myeloma, gastrointestinal malignancies, the acquired immunodeficiency syndrome-related Kaposi's sarcoma and refractory ovarian cancer.[2] It rarely causes side-effects like cardiotoxicity or hair loss, but frequently results in many kinds of mucocutaneous reactions. One of its major toxic effects is stomatitis, which was found to be the dose-limiting factor for the maximal single dose and was less dependent on schedule. Most patients experienced only minor toxic effects and did not require dose modifications.[1]Iqbal S et al reported 2 of 32 patients with advanced solid tumors treated with pegylated liposomal doxorubicin and docetaxel who experienced stomatitis, anorexia,

esophagitis and neutropenic fever.[3] However, no details about the severity of the adverse reactions were revealed. Muggia FM et al reported 1 of 43 patients with persistent or recurrent endometrial carcinoma treated with pegylated liposomal doxorubicin who experienced grade 4 toxicities , which were-one episode each of esophagitis, hematuria and vomiting.[4] To our knowledge, grade 4 stomatitis and esophagitis associated with grade 1 PPE induced by pegylated liposomal doxorubicin, just as presented in this case, is really unusual.

It is rarely reported that conventional doses of vincristine and melphalan cause stomatitis or esophagitis. Thus, pegylated liposomal doxorubicin aroused our suspicion. One week after the last infusion of chemotherapy drugs, evidence was furnished as PPE occurred. Finally, no similar symptoms came again when the patient received the second course of chemotherapy (switched from VADM to CTD). All of the above helped us to confirm the final diagnosis in this case. We propose the replacement of stomatitis by oral or gastroesophageal mucous reaction as one of the six skin adverse reactions associated with pegylated liposomal doxorubicin. ❑

REFERENCES

1. Lotem M, Hubert A, Lyass O, Goldenhersh MA, Ingber A, Peretz T, et al. Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. Arch Dermatol. 2000;136:1475-80.
2. Mangana J, Zipser MC, Conrad C, Oberholzer PA, Cozzio A, Knuth A, et al. Skin problems associated with pegylated liposomal doxorubicin-more than palmoplantar erythrodysesthesia syndrome. Eur J Dermatol. 2008;18:566-70.
3. Iqbal S, Tsao-Wei DD, Quinn DI, Gitlitz BJ, Groshen S, Aparicio A, et al. Phase I clinical trial of pegylated liposomal Doxorubicin and docetaxel in patients with advanced solid tumors. Am J Clin Oncol. 2011;34:27-31.
4. Muggia FM, Blessing JA, Sorosky J, Reid GC. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2002;20:2360-4.

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